

A) Before engineering of CH3 domain

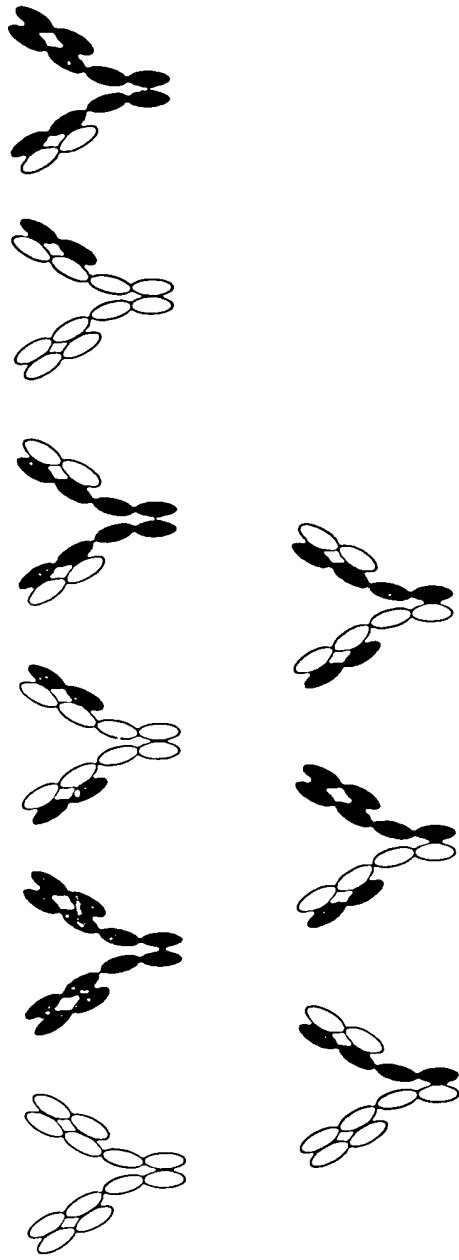


Fig. 1A

B) After engineering of CH3 domain

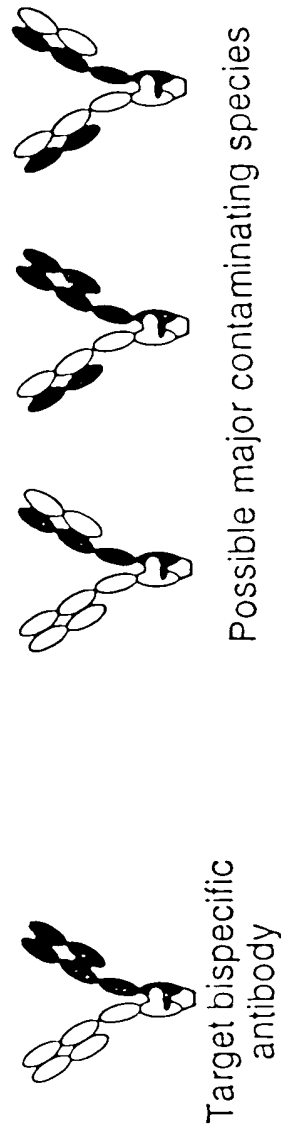
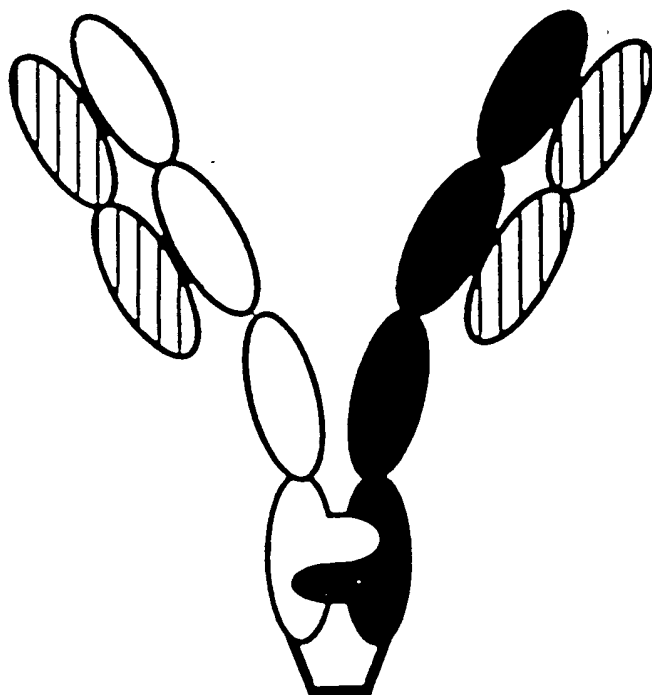


Fig. 1B

~ = Engineered disulfide bond between CH3 domains



Target bispecific
antibody

Fig. 1C

Fig. 2A

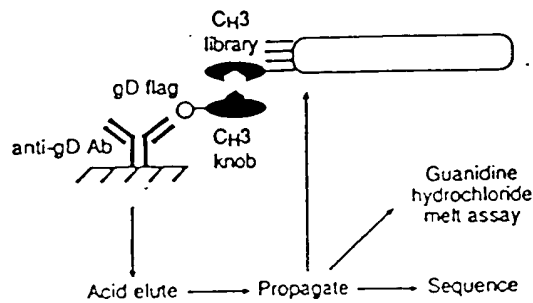


Fig. 2B

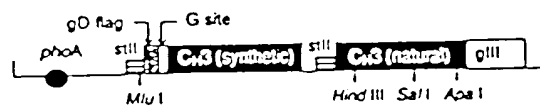


Fig. 2C

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*111      -> gD flag      -> CH3
P A T A L E M A D P H R F R C E D L A A N Y C O P
A A C G C C A C G C T C T C A A A T O O C G A C C G A C C T T T T C T C G T A A G A T C T O G C T C A C A C T A C G C C A G C C
#1411
R E P O V T T L P P S R E E N T E M Q V S L N C L
C C G A A G C T C A G C T G T A T C C T T C C A C C T T C C A G A C A A T C A C T A A A A C C A G C T C T C T C T C T C G C T C
350      360      366
V E C F Y P S D I A V E W E S H C O P E N H Y E T
C T C A A G C T T T C T A T C C G A C C A T A T C C C T C T C A A T O C G A A C C A C C G G T C A A C C G C A A A C A C T A C A A A C C
370      380      390
T P P V L D S D C S F F L Y S E L T V D E S R W O
A C T C C A C C G C T C T C A T T C T C A T O G C T C T T C T T C T A T T C A A G C T C A C C T T C A A A G C C C T T G C C A G
400
O C H V F B C S V H R E A L H P H T T C E S L S L
C A A G C C A C C T T T C A G C T C T C T T A T C C A C C A G C C T T C C A C A C C A C T A C A C C C A A A A G C C T C T C C T C
420      430      440
S P C S O
T C T O C C G C A A T A A G C T C A G C C T C T C T A G A C C T C A G C T C A T T T A T C A A A A A A T A T C G C A T T T C T T C T C
-> #111
A S H F V F S I A T H A T A C O P R E P O V T T L
C A T C T A T C T C T C T T T T C T A T T C T A C A A C C C T A C C T O C C A C C C C A G A C C A C A C C T C A C A C C T C
350      360      366      370
P P S R E E N T E M Q V S L T C L V E C F Y P S D
C C C A T O C C G G A A C A T C A C C A A A C C A G C C A A G C T T C T A C T C T C T C A A A G C C T T C T A T C C A C C A C A
#14111
I A V E W E S H C O P E N H Y E T T T P P V L D S D
T C G C C T C A C T O C C A C A A T O O C A C C C A C A C A C T A C A A C A C A C C C T C C C T C T C A C T O C C A C
380      390      400      410      420
C S F F L Y S F L T V D E S R W O C H V F B C S
G C T C T T C T C T C T A C A C C T T T C A C C C C C A C A C A C C A C C T C C A C C A C C C A C C T T C T C A T T C T C C
430      440      448
V H R E A L H P H Y T O E S L S L S P C R A A C P
T C A T O C A T C A G C C T C T C A C A C C A C T A C A C C A C A A C C C T C C C T C T C T C C C C T A A T A G C C C C C
#1411
T C A T O C A T C A G C C T C T C A C A C C A C T A C A C C A C A A C C C T C C C T C T C T C C C C T A A T A G C C C C C
ApaI

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(SEQ ID NO: 13)

Fig. 3A

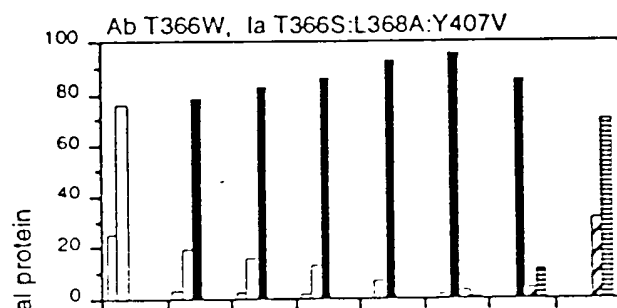


Fig. 3B

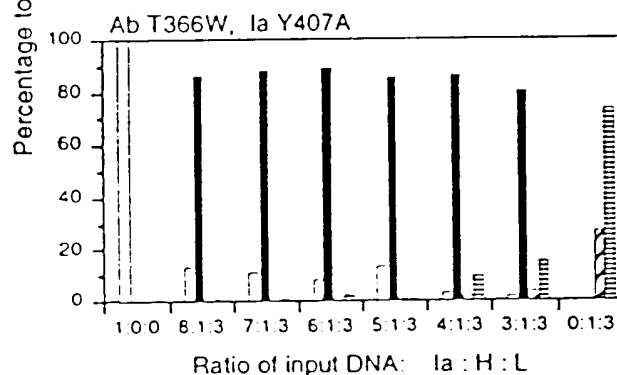


Fig. 3C



		20	abc	30	40	50
1		QSVLTQ	PASV	SGSPGQ	SITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM	IEGSKRPSGV
	Ax1.78	QSVLTQ	PASV	SGSPGQ	SITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM	IEGSKRPSGV
	Rse.23	QSVLTQ	PASV	SGSPGQ	SITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM	IEGSKRPSGV
	IgER.MAT2C1G11	QSVLTQ	PASV	SGSPGQ	SITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM	IEGSKRPSGV
	GCSFR.A4	QSVLTQ	PASV	SGSPGQ	SITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM	IEGSKRPSGV
	Rse.04	QSVLTQ	PASV	SGSPGQ	SITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM	IEGSKRPSGV
	obr.4	QSVLTQ	PASV	SGSPGQ	SITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM	IEGSKRPSGV
	Rse.20	QSVLTQ	PASV	SGSPGQ	SITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM	IEGSKRPSGV
	Rse.15	QSVLTQ	PASV	SGSPGQ	SITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM	IEGSKRPSGV
	veg.f.5	QSVLTQ	PASV	SGSPGQ	SITISCTGTSSDVGGYNYVSWYQQHPGKAPKLM	IEGSKRPSGV
		#####		#####		###
				CDR L1		CDR L2

		60	70	80	90	a	100	
		SNRFSG	SKSGNTASLT	ISGLQAE	ADYCYCSSYT	TRSTRV	FGGG	TKLTVL (SEQ ID NO: 14)
	Ax1.78	SNRFSG	SKSGNTASLT	ISGLQAE	ADYCYCSSYT	TRSTRV	FGGG	TKLTVL (SEQ ID NO: 15)
	Rse.23	SNRFSG	SKSGNTASLT	ISGLQAE	ADYCYCSSYT	TRSTRV	FGGG	TKLTVL (SEQ ID NO: 16)
	IgER.MAT2C1G11	SNRFSG	SKSGNTASLT	ISGLQAE	ADYCYCSSYT	TRSTRV	FGGG	TKLTVL (SEQ ID NO: 17)
	GCSFR.A4	SNRFSG	SKSGNTASLT	ISGLQAE	ADYCYCSSYT	TRSTRV	FGGG	TKLTVL (SEQ ID NO: 18)
	Rse.04	SNRFSG	SKSGNTASLT	ISGLQAE	ADYCYCSSYT	TRSTRV	FGGG	TKLTVL (SEQ ID NO: 19)
	obr.4	SNRFSG	SKSGNTASLT	ISGLQAE	ADYCYCSSYT	TRSTRV	FGGG	TKLTVL (SEQ ID NO: 20)
	Rse.20	SNRFSG	SKSGNTASLT	ISGLQAE	ADYCYCSSYT	TRSTRV	FGGG	TKLTVL (SEQ ID NO: 21)
	Rse.15	SNRFSG	SKSGNTASLT	ISGLQAE	ADYCYCSSYT	TRSTRV	FGGG	TKLTVL (SEQ ID NO: 22)
	veg.f.5	SNRFSG	SKSGNTASLT	ISGLQAE	ADYCYCSSYT	TRSTRV	FGGG	TKLTVL (SEQ ID NO: 22)
		#####		#####		#####		
				CDR L3				

Fig. 4

V_H

her3.18 10 20 30 ab 40 50 a
 QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYEMN--WVRQAPGKGLEWVSGISGSGGSTYY

 EVQLVESGPGLVKPSQTLSTCTVSGGSISGGYYWSWIRQHPGKGLEWIGYIY-YSGSTYY
 obr.26 CDR H1 CDR H2

60 70 80 abc 90 100abcde 110 (SEQ ID NO: 23)
 ADSVKGRFTISRDN SKNTLYLQMNRLRAEDTAVYYCARDNGWELTDWYFDLWGRGTMVTVSS

NPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARVDLEDYGSGASDYWGQGTLTVTSS (SEQ ID NO: 24)
 CDR H2 CDR H3

V_L

her3.18 10 20 30 40 50 60
 DIQMTQSPSTLSASIGDRVTITCRASEGIYHWLAWYQQKPGKAPKLLIYKASSLASGAPSRF
 obr.26 CDR L1 CDR L2

70 80 90 100 (SEQ ID NO: 25)
 SGSGSGTDFTLTISSLQPD FAYYCCQYSNYPLTFGGGTKLEIK
 CDR L3

Fig. 5

Percentage Identity of anti-ObR and anti-HER3 V_L

	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11
O1	49	47	51	81	60	48	76	51	100	62	51
O2	84	79	88	50	48	99	48	88	48	45	88
O3	83	82	85	51	50	95	49	85	49	46	85
O4	47	50	51	83	77	48	65	51	73	64	51
O5	49	47	51	81	60	48	76	51	100	62	51
O6	83	79	86	50	50	99	47	86	48	45	86
O7	81	100	86	51	49	80	48	86	47	44	86
O8	81	100	86	51	49	80	48	86	47	44	86
O9	81	100	86	51	49	80	48	86	47	44	86
O10	83	79	85	50	49	98	46	85	48	45	85
O11	83	80	87	50	49	99	47	87	48	45	87
O12	81	100	86	51	49	80	48	86	47	44	86
O13	49	47	51	81	60	48	76	51	100	62	51
O14	50	50	54	95	67	49	76	54	75	62	54
O15	82	79	85	49	48	97	46	85	47	44	85
O16	84	80	87	50	49	100	47	87	48	45	87
O17	45	44	47	65	62	45	62	47	62	100	47
O18	50	51	50	75	79	50	63	50	66	62	50

O1-O18: Anti-Ob-R antibody clones obr. 1, 11, 12, 14, 15, 16, 17, 18, 19, 2, 20, 21, 22, 23, 24, 26, 3, 4, respectively.

H1-H11: Anti-HER3 antibody clones her3.1, 3.10, 3.11, 3.12, 3.16, 3.18, 3.19, 3.22, 3.3, 3.4, 3.7, respectively.

Fig. 6